Antivirals in Development for CMV Prevention in HSCT Recipients

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CMV in HSCT Recipients

- CMV infection and disease associated with considerable mortality and morbidity in HSCT recipients

- CMV infection common in first 100-days following HSCT
  - ~70% in certain high-risk patients (recipient CMV serology positive, with or without donor CMV serology positive [R+/D- or R+/D+])
  - Without prevention 20-35% progress to disease

- Two preventive strategies used
  - Prophylaxis
  - Preemptive therapy (PET): the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected

Unmet Medical Need for a Novel anti-CMV agent

- All currently available anti-CMV agents associated with unacceptable toxicities¹
  - GCV/VGCV: myelotoxicity
  - Foscarnet: nephrotoxicity
  - Cidofovir: both

- PET is the preferred prevention modality worldwide²

- HSCT population any level of viremia associated with increased overall and non-relapse mortality, even after adjusting for PET³, ⁴

- Unmet need for a safe and efficacious agent for CMV prophylaxis

New Anti-CMV Approaches in Development

- ganciclovir
- foscarnet
- cidofovir
- maribavir
- brincidofovir
- letermovir

DNA synthesis (DNA polymerase)

Cleavage & Packaging

Maturation

Entry

Egress

Courtesy Karl S. Peggs
Stratification: transplant conditioning and CMV serostatus R
90 Centers

Randomization
Maribavir: placebo 454:227

Sample Size

CMV disease confirmed by the endpoint committee

Primary Endpoint

Pre-emptive Treatment per center standard

Study Drug Treatment
weekly assessments
CMV disease and Safety

Follow up

CMV disease confirmed by the endpoint committee

Primary Endpoint

Maribavir: Phase 3 Trial design

Maribavir: Phase 3 Trial design

Maribavir: Phase III trial results

Maribavir: Phase III trial results

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**CMV disease**

- **Event-free probability**

  - **Log-rank p=0.74**
  - **HR 0.88 (0.42-1.84)**

  **Number at risk**
  - Maribavir: 454, 438, 413, 400, 381, 361, 343
  - Placebo: 227, 207, 197, 191, 187, 179, 171

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**All-cause mortality**

- **Event-free probability**

  - **Log-rank p=1.16 (0.78-1.69)**

  **Number at risk**
  - Placebo: 223, 211, 201, 195, 190, 184, 176

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**CMV infection (pp65 antigen)**

- **Event-free probability**

  - **Log-rank p=0.02**
  - **HR 0.73 (0.56-0.96)**

  **Number at risk**
  - Maribavir: 454, 364, 322, 299, 281, 257, 245
  - Placebo: 227, 161, 138, 128, 119, 111, 103

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**CMV infection (DNA PCR)**

- **Event-free probability**

  - **Log-rank p=0.55**
  - **HR 0.92 (0.70-1.21)**

  **Number at risk**
  - Maribavir: 454, 361, 321, 295, 277, 254, 242
  - Placebo: 227, 164, 145, 137, 129, 124, 117

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Current Opinion in Virology
Brincidofovir: Phase 3 SUPPRESS Trial Design

- **Population:** CMV seropositive allo-HCT recipients
- **Primary endpoint:** CMV infection requiring the initiation of preemptive therapy through Week 24
- **Design:** Superiority vs. current standard of care (placebo and monitoring)
- **Power:** >85% power to detect 50% reduction in CMV events vs. placebo
- **Dosing:** Began when patient can swallow tablet; twice-weekly through Week 14

Oral Presentation at BMT Tandem Meeting, Feb 2016
Fewer Subjects Reactivated CMV During On Drug

24% BCV vs. 38% placebo
p=0.002
More Infections Occurred During Off-drug Period

Treatment Period

24% BCV vs. 38% placebo
p=0.002

Follow-Up Period

22% BCV vs. 11% placebo
p=0.06
GVHD events on BCV were predominantly the gut, not skin, suggesting the diagnosis was driven by diarrhea.

<table>
<thead>
<tr>
<th>GVHD Stage</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>49 (16.2)</td>
<td>3 (1.0)</td>
<td>88 (29.0)</td>
<td>24 (16.1)</td>
<td>1 (0.7)</td>
<td>28 (18.8)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>42 (13.9)</td>
<td>14 (4.6)</td>
<td>40 (13.2)</td>
<td>18 (12.1)</td>
<td>0</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>22 (7.3)</td>
<td>7 (2.3)</td>
<td>33 (10.9)</td>
<td>8 (5.4)</td>
<td>3 (2.0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0</td>
<td>6 (2.0)</td>
<td>13 (4.3)</td>
<td>0</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

_the median cumulative exposure to corticosteroids was 8-fold higher in subjects on the BCV arm than those on placebo_
Summary of the SUPPRESS (Phase 3) Trial Results

- During the on-treatment period through Week 14 after HCT:
  - Fewer subjects in the brincidofovir arm had CMV reactivation

- During the 10 weeks off-treatment from Week 14 to Week 24:
  - An increase in CMV infections was observed in subjects randomized to BCV

- At Week 24, a numerical but non-statistically significant increase in mortality was noted in subjects randomized to BCV

- CMV infections and mortality in the brincidofovir arm were driven by diagnoses of GVHD and a significantly higher use of corticosteroids and other immunosuppressive agents than in the control arm
Clinical Trial Design for CMV Prophylaxis

**Study Day 0**

- **Study Therapy**
  - 10-14 weeks on treatment depending on randomization date

- **Randomization window**
  - within 28 days post-transplant

**Transplant**

- **Randomization**
  - 2:1
  - Stratified by risk and study site

- **Letermovir Arm, N=373**
  - 480 mg QD or 240 mg QD +CsA

- **Placebo Arm, N=192**
  - Placebo QD

**Follow-up**

- **Week 14**
  - Post-transplant
  - End of study therapy

- **Week 24**
  - Post-transplant
  - Initial dataset

- **Week 48**
  - Post-transplant
  - Final visit

**Primary Endpoint**

- **Long-term follow up**

**Study Day 0**
P001: Primary Efficacy Endpoint

**Primary endpoint**

- The proportion of HSCT recipients with clinically significant CMV infection through Week 24 (~6 months) post-transplant, defined as the occurrence of:
  
  - CMV end-organ disease

OR

- Initiation of anti-CMV pre-emptive treatment (PET) based on documented CMV viremia (any detectable viral load using the central laboratory CMV DNA PCR assay) and the clinical condition of the patient
**P001: Primary Endpoint: Proportion of Subjects Who Failed Prophylaxis, (NC=F Approach, FAS Population)**

Proportion of subjects who failed prophylaxis through Week 24 post-transplant was significantly lower in the letermovir group

<table>
<thead>
<tr>
<th>Reasons for failure</th>
<th>Letermovir (N=325)</th>
<th>Placebo (N=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects who failed prophylaxis (primary endpoint)</td>
<td>122 (37.5)</td>
<td>103 (60.6)</td>
</tr>
<tr>
<td>Clinically significant CMV infection by Week 24</td>
<td>57 (17.5)</td>
<td>71 (41.8)</td>
</tr>
<tr>
<td>Initiation of PET based on documented viremia</td>
<td>52 (16.0)</td>
<td>68 (40.0)</td>
</tr>
<tr>
<td>CMV end-organ disease</td>
<td>5 (1.5)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Discontinued from study before Week 24</td>
<td>56 (17.2)</td>
<td>27 (15.9)</td>
</tr>
<tr>
<td>Missing outcome in Week 24 visit window</td>
<td>9 (2.8)</td>
<td>5 (2.9)</td>
</tr>
</tbody>
</table>

**Stratum-adjusted treatment difference (Letermovir-Placebo)**

<table>
<thead>
<tr>
<th>Difference (95% CI)</th>
<th>Letermovir (N=325)</th>
<th>Placebo (N=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-23.5 (-32.5, -14.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value <0.0001

† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

NC=F, Non-Completer = Failure
Time to onset of clinically significant CMV infection is substantially different between letermovir and placebo arms through Week 24 post-transplant.

Stratified log-rank test, Two-sided p-value <0.0001

- **Placebo**
  - 15% at Week 0
  - 44.3% at Week 24

- **Letermovir**
  - 6.8% at Week 0
  - 18.9% at Week 24
All-cause mortality is significantly lower in the letermovir group.

Stratified log-rank test,
Two-sided p-value = 0.0327
Data (includes 90% of patients) at Week 48 post-transplant shows significant difference in all-cause mortality between letermovir and placebo.

Stratified log-rank test, 
p-value = 0.0189
P001: AE Summary through Week 24 Post-transplant (ASaT)

Overall, the AE profile was similar in letemovir and placebo groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Letemovir</th>
<th>Placebo</th>
<th>Difference vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>% Estimate (95% CI)</td>
</tr>
<tr>
<td>Subjects in Population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ≥1 AE</td>
<td>373 (98)</td>
<td>192 (100)</td>
<td>-1.9 (-3.8, 0.1)</td>
</tr>
<tr>
<td>with no AE</td>
<td>7 (2)</td>
<td>0 (0)</td>
<td>1.9 (-0.1, 3.8)</td>
</tr>
<tr>
<td>with ≥1 drug-related (DR) AE</td>
<td>63 (17)</td>
<td>23 (12)</td>
<td>4.9 (-1.4, 10.6)</td>
</tr>
<tr>
<td>with ≥1 serious AE (SAE)</td>
<td>193 (52)</td>
<td>109 (57)</td>
<td>-5.0 (-13.6, 3.7)</td>
</tr>
<tr>
<td>with ≥1 DRSAE</td>
<td>3 (1)</td>
<td>3 (2)</td>
<td>NA</td>
</tr>
<tr>
<td>who died</td>
<td>61 (16)</td>
<td>38 (20)</td>
<td>-3.4 (-10.5, 3.1)</td>
</tr>
<tr>
<td>discontinued due to an AE</td>
<td>72 (19)</td>
<td>98 (51)</td>
<td>-31.7 (-39.7, -23.6)</td>
</tr>
<tr>
<td>discontinued due to a DRAE</td>
<td>18 (5)</td>
<td>7 (4)</td>
<td>1.2 (-2.9, 4.5)</td>
</tr>
<tr>
<td>discontinued due to a SAE</td>
<td>35 (9)</td>
<td>27 (14)</td>
<td>-4.7 (-10.9, 0.7)</td>
</tr>
<tr>
<td>discontinued due to DRSAE</td>
<td>3 (1)</td>
<td>3 (2)</td>
<td>NA</td>
</tr>
</tbody>
</table>
**P001: Most Common AEs (Through Week 24 Post-Transplant, ASaT)**

*Most common AEs reported were as expected in this patient population and similar between letermovir and placebo*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Letermovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects in Population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ≥1 AE</td>
<td>366 (98)</td>
<td>192 (100)</td>
</tr>
<tr>
<td>with no AE</td>
<td>7 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>272 (73)</td>
<td>137 (71)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>105 (28)</td>
<td>52 (27)</td>
</tr>
<tr>
<td>Nausea</td>
<td>102 (27)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>74 (20)</td>
<td>32 (17)</td>
</tr>
<tr>
<td><strong>General/Administration Conditions</strong></td>
<td>223 (60)</td>
<td>111 (58)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>86 (23)</td>
<td>50 (26)</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>173 (46)</td>
<td>102 (53)</td>
</tr>
<tr>
<td>Graft vs. Host Disease</td>
<td>166 (45)</td>
<td>95 (49)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>264 (71)</td>
<td>145 (76)</td>
</tr>
<tr>
<td>CMV Infection</td>
<td>62 (17)</td>
<td>90 (47)</td>
</tr>
<tr>
<td><strong>Skin &amp; Subcutaneous Tissue disorders</strong></td>
<td>186 (50)</td>
<td>93 (48)</td>
</tr>
<tr>
<td>Rash</td>
<td>86 (23)</td>
<td>48 (25)</td>
</tr>
</tbody>
</table>
**P001: Drug-related AEs in ≥1% Subjects (Through Week 24 Post-Transplant, ASaT)**

*A relatively low number of drug-related AEs were reported*

<table>
<thead>
<tr>
<th>Category</th>
<th>Letemovir n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects in population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ≥1 drug-related AE</td>
<td>373 (17)</td>
<td>192 (12)</td>
</tr>
<tr>
<td>with no drug-related AE</td>
<td>310 (83)</td>
<td>169 (88)</td>
</tr>
<tr>
<td><strong>Blood &amp; Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (7)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>General/Administration Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT) increased</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) increased</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Renal &amp; Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Skin &amp; Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (0.3)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
P001: Hematological Analyses

- **No evidence of myelotoxicity**
  - Hematological lab parameters similar between letermovir and placebo
  - More than 60% of subjects had not engrafted at baseline:
    - Incidence of engraftment similar between letermovir (95%) & placebo (91%)
    - Median time to engraftment similar between letermovir (19 days) & placebo (18 days)

![Graph showing cumulative rate of engraftment](image)

Letermovir vs Placebo
Stratified log-rank test, two-sided p-value = 0.1047

Cumulative Rate of Engraftment (%)

Weeks Post-Transplant
Letermovir is highly efficacious in preventing clinically significant CMV infection through Week 24 post-transplant

- ~40% relative reduction compared to placebo
  - Number needed to treat (NNT): 5 patients
- Efficacy demonstrated across a broad range of subgroups
- ~33% relative risk reduction in mortality compared to placebo
  - Mortality benefit continues through Week 48
  - NNT: 18 patients

Letermovir is generally well tolerated

- AE profile similar to placebo
- No evidence of myelotoxicity, nephrotoxicity or hepatotoxicity
Thank you!